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Case Management and Clinical Outcomes of People Living with HIV and Admitted to a State-aided District Hospital in Durban, South Africa in 2007

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DECLARATION

I, Dr. Henry Sunpath declare that

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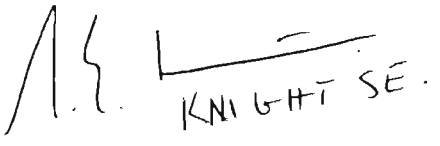
Supervisors Signature: 

Dr Stephen Knight

ABSTRACT

Title: Case Management and Clinical Outcomes of People Living with HIV and Admitted to a State-aided District Hospital in Durban, South Africa in 2007.

Introduction: A proportion of the many patients who have advanced AIDS in South Africa present for the first time requiring admission to hospital, the number of which are limited by the availability of beds. Novel ways were developed to offer subacute inpatient care at *Siyaphila,* a facility linked to McCord Hospital in Durban to provide expedited or immediate antiretroviral therapy (ART) (exposed) for patients with advanced disease before their discharge (ART group) . Different components of palliative care were offered for those who did not enter the inpatient ART programme or who were terminally ill (non-ART group) (non-exposed).

Aim: The aim of the study is to describe the clinical condition, inpatient case management and outcomes before discharge of people living with HIV admitted to *Siyaphila* in order to assist in developing appropriate protocols for inpatient care.

Methods: This was an observational, analytic, cohort study using a convenience sample of all patients consecutively admitted to *Siyaphila* during nine months in 2006/2007. Prevalence of AIDS defining conditions at *Siyaphila*, time taken to progress from one stage of care to another and outcomes for the two groups before discharge were determined. Univariate and multivariate logistic regression analysis was performed on the ART group to identify risk factors for mortality before discharge. A comparison between the ART and non-ART group was also undertaken.

Results: Among the cohort of 405 PLHIV enrolled at *Siyaphila* during the study period only 171 (42%) were initiated on ART immediately. In all patients, tuberculosis (251; 62%) was the most common opportunistic infection followed by cryptococcal meningitis (68; 17%) and *Pneumocystis* pneumonia (28; 7%). The mean baseline CD4 cell count was 84 cells/uL for the non-ART group and 55 cells/uL for the ART group. ($p < 0.01$) The median time from initial admission until discharge was 13 days in the non-ART group and 18 days in the ART group. The mortality before discharge among the non-ART group was

24% compared to 6% among the ART group. (p =0.001). The median number of days before ART was initiated was 14 days. Immune reconstitution inflammatory syndrome was diagnosed in seven patients (4%) among the admissions but caused no deaths. In the multivariate analysis, the odds ratio for mortality for patients under 40 years was 0.1 (95% Confidence Interval: 0.01 – 0.9).

Conclusions: Subacute care offered at *Siyaphila* provides an entry point into the ART programme for non-ambulatory patients who in the KwaZulu-Natal context have low ART uptake after discharge. The findings of this study should be adopted as the best clinical practice for PLHIV and AIDS admitted in the late stages of the disease. (Words 423)

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AIDS:	Acquired Immunodeficiency Syndrome
ART:	Antiretroviral Therapy
HIV:	Human Immunodeficiency Virus
HRSA:	Health Research Services Administration
IRIS:	Immune Reconstitution Inflammatory Syndrome
ICU:	Intensive Care Unit
OI	Opportunistic Infections
PLHIV:	People Living with HIV
WHO:	World Health Organization

1 CHAPTER 1: INTRODUCTION

In South Africa, little is known about how the public-funded district hospitals are coping with the increased demand for inpatient care from the widespread epidemic of people living with Human Immunodeficiency Virus (PLHIV) and Acquired Immune Deficiency Syndrome (AIDS). Due to stigma, denial and poor socioeconomic circumstances many PLHIV present to hospitals in an advanced stage of illness. There are also limits to the number of patients who can be accommodated for initiation of antiretroviral therapy (ART) in outpatient clinics. Novel ways need to be found to provide access to ART for all PLHIV including those presenting to the hospital for admission of intercurrent opportunistic infections or with advanced AIDS disease who are not on ART. Early or expedited ART for the purpose of this study is defined as the inpatient provision of ART for Stage 4 disease soon after diagnosis and / or management of the AIDS-related conditions during hospitalisation.

The HIV and AIDS National Strategic Plan for South Africa provides framework to be implemented nationally and to begin to slow down the epidemic by 2011.[1] There are operational issues like infrastructure development and staffing around scale up which need development, ongoing monitoring and evaluation.[1] A proportion of patients present for the first time to acute care hospital services with advanced AIDS disease. Clinicians could use this opportunity to initiate these patients on ART. It may be difficult to do this in a busy acute care ward. Such patients could be transferred to a subacute care facility for this phase of their care. This facility could be an in-house unit linked to the acute care ward. There is no available literature describing this type of care for patients with AIDS in South Africa. The concept of subacute care wards (otherwise called step-down care) is supported by the National Department of Health as a way of reducing congestion in the acute care medical wards of hospitals. *Siyaphila* is an inpatient facility, which is linked to the acute care medical wards and offers subacute care for people living with advanced HIV and AIDS. *Siyaphila* offers a package of healthcare at lower costs than in the acute medical facility and incorporates a holistic care model.

1.1 BACKGROUND

McCord Hospital is a State-aided district hospital in central Durban. It provides services to patients from Durban and surrounding areas, in KwaZulu-Natal. The hospital serves a population from a mixed socio-demographic background. Approximately 2400 patients with AIDS-related illness are admitted to the acute care medical wards at the hospital per year.[2] Patients who are managed at McCord Hospital pay subsidised fees for health care, but this is affordable only to those who have an income or who have some form of financial support from relatives. Patients who cannot afford fees to be admitted to McCord Hospital or the subacute care facility, *Siyaphila,* are referred to other hospitals in the district.

Over the last ten years, McCord Hospital has adapted its vision to provide a comprehensive care plan to focus on the needs of PLHIV in the community it serves. In 2006, approximately 50% of patients admitted to the medical wards were HIV-infected. The majority of these patients were admitted with World Health Organization (WHO) stage 4 AIDS disease.[2] In 2007, the average length of stay of all patients admitted to the acute care medical ward was 10 days, a factor that constrained the number of new PLHIV that could be admitted to this already limited 45-bed ward.[2]

Murphy *et al.* reported high in-hospital mortality in the medical wards at McCord Hospital in 2006 and 2007.[3] In addition; only a small proportion of those living with HIV commenced ART after discharge and they experienced a high mortality even after treatment for opportunistic infections (OI), especially among those with advanced disease. [3] Due to the findings of this study, a new subacute care facility, *Siyaphila* ("We are well" in Zulu), was commissioned in May 2006 at McCord Hospital. The purpose of this facility is to offer subacute care to those who survive the initial admission with advanced stage AIDS-related disease. These patients often require prolonged treatment of their opportunistic infections and other intercurrent systemic illnesses and accompanying physical and psychosocial co-morbidities. These acutely ill 'survivors' are thus transferred from the acute care medical wards to *Siyaphila*. There is consequently a reduction in the length of stay in acute care ward and opening up of beds at McCord

Hospital for new acutely ill patients to be admitted. This programme enables patients to be managed at lower costs than in acute care medical wards.[2]

Siyaphila offers a package of healthcare at lower costs and incorporates the following components:

Clinical Care: Providing clinical care to PLHIV restores and maintains their immune status and mitigates the physical consequences of AIDS-related disease. A key component of clinical care is initiating PLHIV on antiretroviral therapy.

Spiritual Care: A team competent in spiritual care addresses the major life events that cause people living with HIV to question themselves, their purpose and their meaning in life.

Psychological Care: A psychologist and visiting psychiatrist address the non-physical suffering of people living with HIV and that of their family members. The team assesses cognitive disorders and AIDS-related dementia prior to starting ART and again after two months of therapy.

Social Care: The social work team assists individuals and family members in maintaining linkages to and use of care, thereby preventing further HIV transmission ensuring adherence to treatment. Group support services are also offered to PLHIV.

Physical Rehabilitation: Physical therapy and nutritional interventions are important elements of successful rehabilitation.

End-of-Life Care: The purpose of end-of-life care is to ensure a good quality of life through symptom management and supportive care through the terminal phase of AIDS-related illness in the patient and bereavement counseling for the family.

HIV Counseling Services: A team of dedicated HIV counselors is involved in ART literacy training before and after ART initiation. ART literacy training is conducted in three sessions that involve counseling and education of patients around three key areas, namely, clinical aspects of HIV infection, ART adherence and the development of healthy

lifestyle skills. The counseling takes place with individuals and their family members before ART initiation. The content is similar to the counseling done in the outpatient clinic. There is additional emphasis on finding and training a suitable treatment supporter. As the patient is very ill, the first few weeks of care requires directly observed treatment even after the patient is discharged.

Community Support and Follow-up: Patients who do not initiate ART at *Siyaphila* are followed up by linking them to different care providers and programmes near their place of residence. Clinics that provide ongoing care for PLHIV are listed on several national databases. Patients from the eThekwini Municipality are also referred to government or private sector hospitals for clinical follow up or ART initiation.

Since May 2006, approximately 50 patients with advanced AIDS disease have been admitted to *Siyaphila* monthly for ongoing subacute care. Patients were admitted for the continuation of treatment of various medical conditions commenced in the acute care ward. Some of the patients are initiated on ART as a medical emergency shortly after commencing treatment for an opportunistic infection. These patients have WHO Stage 4 disease and / or a CD4 cell count of less than 200 cells/uL, but are able to take treatment orally. Other patients are identified for terminal care by the palliative care team, in consultation with their next-of-kin. Palliative care requires time and care from a highly specialised team that is based at *Siyaphila*.[4]

From November 2006, approximately 20 patients monthly have commenced ART whilst admitted to *Siyaphila*. A system was implemented with advice from medical consultants in HIV and AIDS medicine at McCord Hospital. This triage system was used to assist junior and less experienced clinicians determine which medical inpatients could be cared for with subacute, but with the AIDS-specific inpatient care offered at *Siyaphila.* These patients are offered one of the two protocols of care, after informed discussion with them and their next-of-kin and are categorised as either a non-ART (non-exposed) or an ART (exposed) group.

(1) Non-ART group: In this group, PLHIV are offered terminal care if they have irreversible end-organ damage, advanced malignancies or are unable to tolerate oral medication for various irreversible medical reasons. The conditions for which ART alone is not recommended include end-stage renal disease with multiple co-morbidities, advanced malignancies (Kaposi's sarcoma. lymphoma, cancer of the cervix), intractable cardiac failure with cardiomyopathy, pulmonary hypertension with poor prognostic features; severe soft tissue sepsis, and complicated central nervous system infections with a poor prognosis. A proportion of patients were not offered ART as they lived outside the eThekwini municipality or had insufficient funds to afford the cost of at least a two-week inpatient stay in the hospital. These very sick PLHIV were referred to other ART sites of their choice for further care.

Some patients in the non-ART group are offered palliative care depending on their clinical condition during hospitalisation. The different aspects of palliative care include ongoing treatment of the presenting infection, pain and symptom management and psychosocial support specifically addressing the needs of PLHIV. For successful AIDS management, a combination of disease specific and palliative care therapies are required. "Palliative care in AIDS is defined as supportive care that improves the quality of life and involves an interdisciplinary team of biomedical and psychosocial care providers".[4] A palliative care plan for each patient ideally begins at the time of diagnosis of a potentially fatal illness or at the time of first contact, and continues together with disease specific care and throughout life. Effective disease specific treatment includes the treatment and prevention of opportunistic infections and use of ART where appropriate. In addition, symptom control and alleviation may improve the outcome of those living with HIV related disease and reduce their mortality. If the patient deteriorates clinically despite medical care, the terminal care is offered to those with irreversible medical conditions.

(2) ART group: This group of PLHIV and AIDS admitted to *Siyaphila* received ongoing care of treatable, concomitant clinical conditions. Patient care was further improved by expedited commencement of ART before discharge. These PLHIV were initiated on ART at *Siyaphila* based on the clinical and social criteria advocated in the 2004

Department of Health HIV/AIDS Treatment Guidelines and had WHO Stage 4 disease and recorded a CD4 count <200 cells/uL.[1]

In addition, certain *Siyaphila* specific criteria have to be adhered to.[2] For inpatient ART initiation these PLHIV should reside in the greater Durban area or eThekwini Municipality, disclose their HIV status to at least one person who could then be a treatment supporter (especially as most patients were non-ambulatory), be able to swallow pills and afford the cost of admission to *Siyaphila* for at least two weeks.

1.2 AIM AND OBJECTIVES OF THE RESEARCH

The aim of the study is to describe the clinical conditions, inpatient case management and outcomes of a cohort of people living with HIV, who were admitted for subacute care to *Siyaphila* during nine months in 2006/2007.

The objectives of the study are:

1) To describe the demographic and disease profile of PLHIV admitted to *Siyaphila;*

2) To measure the inpatient prevalence of AIDS-defining conditions in people living with HIV adults admitted for subacute care to *Siyaphila*; and

3) To compare clinical outcomes of the ART (exposed) and non-ART (non-exposed) group at the time of discharge of this cohort of PLHIV from *Siyaphila*.

1.3 SUMMARY OF CHAPTER

The two types of subacute care offered at the *Siyaphila* inpatient facility *at* McCord Hospital involve ART for those recovering from acute opportunistic infections (ART group), or different aspects of palliative care for those not eligible for ART for a range of medical and other reasons (non-ART group). In this model of care, patients that are very ill with HIV and AIDS could continue to receive inpatient care until commencement of ART becomes a viable therapeutic option for them.

2 CHAPTER 2: LITERATURE REVIEW

2.1 INTRODUCTION AND PURPOSE OF REVIEW

There are no guidelines or published reports of how patients are managed in step down care units for patients living with HIV. The *Siyaphila* model of subacute care seeks to combine best practice guidelines from different systems of inpatient care and incorporate them with a policy of expedited ART initiation for very ill patients. The review of the literature begins by describing different systems of inpatient care, and then focuses on specific guidelines for ART initiation with different opportunistic infections. Most of the systems of care reported describe inpatient management of PLHIV requiring ART in different clinical settings in South Africa and other low-income countries. Other studies reviewed give guidelines for the timing of ART initiation, early after diagnosis of an opportunistic infection that has been conducted in outpatient settings. Similar principles of early ART initiation can be operationalised in the inpatient programme at *Siyaphila*.

Several studies have been conducted recently in South Africa to assess the role of ART in PLHIV after diagnosis of an opportunistic infection.[5, 6] These reports have filled a gap in our understanding that studies in high-income countries failed to achieve.[7] The incidence of opportunistic infections varied in different countries and many of these studies did not include the opportunistic infections more commonly occurring in South Africa. In all these studies, ART was the medical intervention that consistently demonstrated the most dramatic improvement among those treated as inpatients and surviving AIDS.[8, 9, 10]

Some studies that examine the provision of ART in the outpatient setting have reported poor outcomes because of delayed initiation of ART generally in any setting for various reasons.[11, 12, 13] In countries where ART demand has exceeded supply, significant pre-ART mortality has occurred among PLHIV awaiting ART. These deaths were related to late entry of the patient into care, a factor that may have been due to patient related factors, health system delays, or inappropriate treatment criteria and protocols.[12] The

lessons learnt from such studies can be applied in such a way to the inpatient model of care to improve the outcomes due to delayed ART initiation. The principles of successful expedited inpatient ART initiation that have been described in this review has been operationalised in the *Siyaphila* model of care. This is the reason why the literature review is written in its current format and content.

2.2 STUDIES ABOUT SYSTEMS OF INPATIENT ART CARE

Criteria for the implementation of expedited ART initiation were outlined in the South African Clinicians Society Journal and in the national "Comprehensive Care, Management and Treatment plan", in January 2009.[11] The guidelines set out which patients qualified for urgent ART. The document recommends that all HIV infected patients should be offered a clinical staging of their disease and CD4 count assessment at the first visit. Hospitalised and all TB patients should have this assessment within one week of CD4 count testing. Patients that need expedited ART could include all adults with a CD4 < 100 cells/uL, all adults with unexplained fever and ongoing loss of weight, all pregnant women qualifying for ART and all adults recently hospitalised with an HIV-linked condition, including TB. This group of very ill patients admitted to a hospital has been reported to present with unique challenges to clinicians when considering initiating treatment. Co-morbid illnesses, potential drug interactions, drug toxicities, immune reconstitution inflammatory syndrome (IRIS) and high pill burdens have been reported to complicate management and have to be taken into consideration.[12] In such cases, it has been recommended that ART be commenced only after treatment for the opportunistic infection has been commenced. Some of the factors described above that could contribute to adverse outcomes after ART initiation have to be managed before discharge. This will require a short stay in the wards after ART initiation.

The consequences of delayed initiation of ART in patients admitted to an acute care ward were investigated by Murphy *et al.* at McCord Hospital in Durban between December 2006 and August 2007.[3] The study was a prospective evaluation of ART uptake (secondary outcome) and mortality (primary outcome) six months after acute admission of PLHIV for an opportunistic infection. At discharge patients with an AIDS-defining illness

or CD4 count <200 cells/uL were urged to seek outpatient ART. All patients underwent a readiness to initiate ART education programme, and were assisted in locating clinics where they could obtain ART. The opportunistic infection recorded among the 50 patients enrolled was tuberculosis in 65% of the patients (pulmonary 29%, extra pulmonary 29%, meningitis 8%), *Pneumocystis* pneumonia (8%), chronic diarrhoea (8%), bacterial pneumonia (8%), cryptococcal meningitis (6%) and toxoplasmosis (4%). Among the 25 patients (50%) who did not initiate ART, 13 died within six months (mortality 52%). Patients with the most advanced disease (CD4 count <50 cells/uL) were least likely to initiate ART by 6 months. This pilot study was undertaken in a group that was similar to that under investigation in this study. The pilot study group could thus be characterized as a historical control group for this study. Recommendations made in this pilot study by the authors, who include the researcher, prompted the creation of the inpatient model of care at the McCord Hospital – *Siyaphila* subacute care centre. This study emphasized the urgent need for creating inpatient systems and defining criteria for expedited ART access for people living with HIV and AIDS.

In 2007, Jameson described the use of an in-patient palliative care unit in Grahamstown to care for patients discharged with AIDS from an acute inpatient ward.[8] The palliative care unit was accessible to patients suffering from cancer and AIDS. Palliative care measures together with the provision of ART were shown to reduce the death of patients with AIDS admitted to the palliative care medical unit. In the first three months, 51 patients were admitted to the inpatient unit. Of these patients, 36 (70%) had AIDS. All the AIDS patients had stage four diseases, and all but three were on ART. While the number of patients was low, it provided an indication of a discernible trend that the mortality in AIDS seemed to be dropping. This may have occurred because ART was being introduced earlier in the very ill patients. The duration of stay in the ward was longer for AIDS patients, and it appears that AIDS patients who survive needed a longer stay in the palliative care unit than cancer patients for their outcomes to improve did. The study was the first in South Africa to report the use of ART among inpatients although ART was commenced before admission. This study furthermore inspired the need to explore how early to introduce ART in an inpatient unit, which remains an important subject.

The principles of the expedited care outlined above were implemented in various inpatient settings. These are described in many different inpatient settings. To evaluate outcomes in patients commencing ART after opportunistic infection treatment during hospitalisation, Eshun-Wilson *et al.* undertook a matched case–control study at a South African academic hospital in Cape Town between January 01, 2004 and March 31, 2008.[5] Controls were selected from patients attending the infectious diseases outpatient department during the same period. Cases were selected from among those patients admitted to the acute care ward. They were initiated on ART as in patients. There was a high risk of loss to follow up in hospitalised patients. Previous studies by Brinkhof *et al.* had suggested that up to 50% of patients who were lost to follow-up in low-resource settings had died.[13] Hospitalised patients who returned for follow-up and remained on ART however, had favourable treatment outcomes, as seen also in a study by Soria *et al.* [14] Both studies have small sample sizes making it difficult to generalise the findings. However, it was possible to have good virological outcomes and adherence in this group of patients commencing ART during hospitalisation. It appeared that a good system of follow up improved outcomes. Patients who do remain in care after discharge from the wards have a comparable treatment outcome to those of more clinically stable patients seen in the outpatient setting. An improved system for patient follow-up and earlier initiation of ART was a recommendation of these studies, a measure designed to improve outcomes in hospitalised patients in these settings.

A retrospective study by Croda conducted in Brazil on 278 HIV-infected patients admitted to a Brazilian intensive-care unit (ICU) between 1996 and 2006 showed that 80% had AIDS-defining conditions, with the most common opportunistic infections being tuberculosis and *Pneumocystis* pneumonia.[10] Mortality was high in both the ICU (55%) and six months after admission (69%). After adjustment for potential confounders, the use of ART in the ICU (whether initiated during admission or previously) was associated with a 50% reduction mortality at 6-months. The benefit was statistically significant only if ART was commenced within the first 4 days after ICU admission. The rate of IRIS that was detected in the ICU was quite low (~1%), but this may be related to the difficulty of identifying IRIS in critically ill patients or from data collected retrospectively. In this study,

mortality was reduced in the first month after ART initiation, an outcome that suggested that, in the setting of acute and severe opportunistic infections, early ART might help to prevent additional opportunistic infections and to control the presenting opportunistic infection. Although confounding could not be ruled out in this retrospective studies, the study contributed to a growing body of evidence supporting the benefits of early ART in patients with acute opportunistic infections, including those admitted to ICU in low income countries.

The community-based programmes like that operating in Keiskamma in South Africa, has ART service nodes linked to community health centres. This inpatient ART programme, as described by Hofmeyer *et al.*[9] is located in a 20-bedded renovated house. The centre provided early ART to the sickest patients who were not able to access ART in the hospital-based programmes. The principles of care were similar to that given to patients who were able to have access to a hospital for management of acute complications. Those who had an opportunistic infection were first treated in the centre where possible. Patients left the centre soon after they had started ART. Bed ridden patients (71/174, 42%) with low Kanofskys score were likely to be sicker and likely to have a higher mortality. Although more patients that are bedridden died, (31 /71, 43%) compared to ambulant patients (5 /103, 5%) the outcome was still considered successful as these patients were extremely ill on commencing therapy and before the ART had a therapeutic effect. The success of the programme was ascribed to having an inpatient facility where expedited ART counseling could be conducted and patients prepared for commencing ART.[8] This study also provided evidence that no one should be regarded as too sick to access ART.

2.3 *EVIDENCE FOR TIMING OF ART INITIATION AFTER ACUTE CARE OF OPPORTUNISTIC INFECTIONS*

How "early" was early ART initiation? This decision seemed to depend on the type of opportunistic infection with which the patient presented. Immediate initiation of ART is recommended for some opportunistic infections for which no specific therapy had been shown to be effective.[15, 16, 17] These conditions include cryptosporidiosis, certain microsporidioses, Kaposi's sarcoma and progressive multifocal leukencephalopathy. For some infections caused by highly drug-resistant pathogens such as multi-resistant herpes simplex virus, immediate initiation of antiretroviral therapy was warranted.[14] In another study by Morris *et al.*, inpatients with severe *Pneumocystis* pneumonia, showed improved survival with early ART initiation.[18]

Two recent randomized trials, by Zolopa *et al.* and by Karim SA *et al.* also supported the use of early ART within sixteen days and eight weeks respectively in patients with acute opportunistic infections.[6, 7] In both trials, the benefits of early ART were apparent within a period of six months. The ACTG study looked at opportunistic infections for which directed therapy was available, and whether antiretroviral therapy should be deferred until the opportunistic infections had been substantially treated or not. The study examined survival among patients with acute opportunistic infections, randomly assigned to early antiretroviral therapy (initiated within 16 days of starting acute opportunistic infection treatment), versus deferred antiretroviral therapy (6 to 12 weeks later). A benefit arising from early initiation of ART was reported in patients with *Pneumocystis* pneumonia, cryptococcal meningitis and toxoplasmosis. [7] Notably, this study of predominately North American patients excluded persons with tuberculosis, a disease that remains a low-incidence opportunistic infection in the United States of America.

To address the question of when to commence treatment in patients with TB, a recently completed randomized, controlled clinical trial by Karim *et al,* from South Africa was conducted.[6] This study suggested that initiating antiretroviral therapy currently with-tuberculosis therapy was also superior to deferral of ART until TB therapy had been completed. Data from this study in Durban recommended starting ART early (within 2

months) after initiation of anti-tuberculosis treatment irrespective of CD4 count.[6] The ideal timing of initiation of ART to maximize benefit and minimize morbidity and mortality remains unclear but has appeared to be within weeks rather than months of initiating anti-tuberculosis treatment. These studies demonstrated conclusively that the presence of an opportunistic infection including TB was not an absolute contraindication to start ART early. Managing AIDS and TB as twin diseases and providing ART as soon as possible will affect the way patients are managed in the wards. Many patients are admitted to the wards with disseminated TB and will greatly benefit from an inpatient ART programme.[6]

Another common opportunistic infection in Southern Africa is cryptococcal meningitis.[20] Delaying ART because of concern about IRIS in these patients had resulted in fatal outcomes, as reported by Bicanic *et al.* in 2000.[21] A randomized study also by Bicanic *et al.* in 2008, showed that AIDS progression or death was lower with early initiation of ART after opportunistic infection than with delayed initiation of therapy.[21] The incidence of IRIS was not increased in those who started ART sooner. It is difficult to predict which patients had a higher mortality among the group not treated with early ART and those treated with ART after antifungal treatment was completed. The inability to accurately prognosticate did not cause clinicians to shy away from initiating ART once the patient had been stabilized on antifungal therapy, particularly because delaying ART could have fatal consequences. The South African HIV Clinicians Society guidelines recommended that clinicians initiate ART between 2 and 4 weeks after starting amphotericin-based treatment, as described by Desdric *et al.*[22] This recommendation is a reasonable approach until ongoing trials provide more evidence about the best way to stagger these two lifesaving therapies. Treatment with amphotericin has to be combined with the appropriate management of raised intracranial pressure.

In summary, there is evidence that ART can be safely and effectively given to all severely ill patients irrespective of their presenting opportunistic infections.

2.4 THE CHALLENGE OF EARLY ART IN THE SICKEST PATIENTS.

Antiretroviral therapy could complicate the clinical scenario by introducing ART-related drug toxicities and drug-drug interactions between ART and antimicrobial therapy prescribed for the opportunistic infection. The WHO report [12] noted that alterations in renal and hepatic function related to the acute opportunistic infection distort ART pharmacokinetics such as metabolic clearance, volumes of distribution, reduced antiretroviral efficacy and increased antiretroviral toxicity. Acute gastrointestinal opportunistic infections decreased antiretroviral drug absorption, producing serum levels that only partially suppressed HIV RNA and thereby generated selection pressure favoring the emergence of antiretroviral drug resistance.[12] Providing ART was thus only the first step in providing quality care, as these patients required close monitoring in the wards post-ART initiation and after discharge to manage these complications of therapy.

2.5 SUMMARY

Several in-patient models of care have been described but none in a district hospital. The pathway of care that was followed in different inpatient settings has been described. The pertinent findings from the survey can be summarized in the following facts. A delay in ART initiation after discharge results in high early mortality. Patients admitted to a palliative care ward after being initiated on ART had better outcomes compared to other terminally ill patients. The National Department of Health guidelines for expedited ART initiation will be difficult to implement for a large number of outpatients. The inpatient group who is very ill will benefit most if the programme is implemented before discharge. There is a high proportion of loss to follow among very ill patients discharged from the medical wards after ART initiation. Therefore, a system of follow up to retain such patients in care is warranted. Commencing ART within four days of admission to an ICU reduced inpatient and six-month mortality. No one should be considered too sick to access ART, as directly observed treatment in a ward can be successfully given. To achieve this there is a need for better follow up and supervision of these patients to detect and manage early complications in the wards.

3 CHAPTER 3: METHODS

3.1 INTRODUCTION

The study used an observational, descriptive, and retrospective study design and was conducted in 2006/2007 at McCord Hospital. The study involved the retrospective analysis of data from a large number of inpatients who were offered expedited ART initiation. In 2006, a prospective pilot study described a similar patient population in the wards of McCord Hospital who were discharged from the wards without ART and followed up for six months after the diagnosis of an AIDS-related opportunistic infection.[3] A high mortality was recorded in this group and so it was not appropriate or ethical to conduct a randomized study. In most of the studies [5, 8, 9] investigating mortality after ART initiation in a hospital ward among very ill patients the data, as in this study, was collected retrospectively.

The aim of the study was to describe the clinical condition, inpatient case management and outcomes of PLHIV admitted during nine months in 2006/2007 considered sick enough to be admitted to a district hospital but transferred for subacute inpatient care, in order to assist in developing protocols to manage the unprecedented burden placed on the acute care medical wards by the HIV and AIDS epidemic in Durban. The McCord-*Siyaphila* facility that offers *s*ubacute care for PLHIV is linked to the acute care medical wards, and was designed as a step-down management facility for patients from acute care wards.

3.2 STUDY SETTING

The study setting was the McCord - *Siyaphila facility* in Durban, which is, located about three kilometers from McCord Hospital. *Siyaphila* has 42 beds and is a well-equipped and modern medical care facility. Doctors from the Department of Medicine at McCord Hospital work at *Siyaphila* on a four-month rotation. There is a multidisciplinary team of carers including social workers, psychologists, nutritionists, nurses and doctors on site.

They provide holistic care for PLHIV, sick enough to be considered for admission to a hospital. A specialist family physician with expertise in AIDS care medicine leads the team together with a doctor trained in palliative medicine. A range of categories of nurses including professional and other nursing staff categories provide nursing care at *Siyaphila, w*hich is also linked to an antiretroviral therapy outpatient treatment site at McCord Hospital.[2] These patients are transferred to *Siyaphila* from the acute care medical wards and managed by the same practitioners. No patients are admitted directly to *Siyaphila* from other hospitals or clinics.

3.3 STUDY POPULATION AND SELECTION

The study population consisted of patients living with HIV who were transferred from the acute care medical wards at McCord Hospital to *Siyaphila* for ongoing subacute inpatient care for various AIDS-related clinical conditions.

3.3.1 Sampling

The study sample was a convenience sample consisting of all patients consecutively transferred from the acute care medical wards at McCord Hospital to *Siyaphila* during a nine-month period.

3.3.2 Inclusion Criteria

All patients older than 18 years of age who were living with HIV and AIDS who were transferred from the acute care wards at McCord Hospital to *Siyaphila* were included in the study population.

3.3.3 Exclusion Criteria

Those excluded from the study population were patients less than 18 years of age and who were pregnant. Pregnant patients requiring inpatient care were admitted into the prevention of mother to child transmission (PMTCT) programme in the antenatal wards.

3.4 DATA MANAGEMENT

3.4.1 Data source and collection

The source of data was obtained from a retrospective record review. Data was extracted from the hospitals electronic database and inpatient clinical records. All data were entered onto a data collection sheet by research volunteers and checked by the principal investigator. The completed data collection forms were examined for completeness of data entry before handing over for data entry into the electronic database.

The data fields collected for each patient included:

- Demographic data;
- CD4 count at time of admission to *Siyaphila*;
- Date of admission to McCord Hospital, date of diagnosis of and type of opportunistic infection or medical problem;
- Dates of admission to *Siyaphila*, of initiation of ART, and of discharge;
- In the case of the death of a patient, the cause of death recorded in the patient record or at the regular hospital mortality reviews were entered; and
- The type of care given and / or management plan , namely:
    - Terminal care and death;
    - ART initiation and early complications; and
    - Discharge home, to a local ART clinic or another institution.

3.4.2 Statistical Processing.

3.4.2.1 Descriptive Statistics:

Numerical data was categorised. An Excel spreadsheet and Access database was used to record all relevant data. The following measures were summarised and presented:

1. Prevalence of different types of opportunistic infections and AIDS-related illnesses;
2. Prevalence of different patient outcomes after admission to *Siyaphila*;

a. Terminal care and death
b. ART initiation at *Siyaphila*
c. Early drug related complications
d. Discharge home without ART
e. Discharge to local clinic for ART or TB treatment
f. Transfer to another institution
g. Refused hospital treatment

3. Cause of death;
4. Duration of inpatient stay for different clinical conditions; and
5. Time to initiation of ART for different conditions.

3.4.2.2 Analytical statistics:

A multivariate logistic regression analysis was performed among patients who initiated ART as inpatients. The outcome used in the model was 'death prior to discharge'. First, a univariate regression analysis was performed including the following covariates: gender; age; baseline CD4 cell count; presence of cryptococcal meningitis (versus other opportunistic infections); baseline albumin; baseline haemoglobin and time between hospital admission and ART initiation (less than 14 days from admission versus greater than 14 days). Next a multivariate logistic regression model was constructed that included age and gender and other variables associated with a p value of <0.05 in the univariate regression model. For each variable in the multivariate model an odds ratio and 95% confidence interval was calculated. Finally, a comparison was made between the two groups (those who initiated ART as inpatients and those who did not receive ART after diagnosis of an acute opportunistic infection) for baseline characteristics and mortality outcome.

3.5 VALIDITY AND BIAS

3.5.1 Measures to ensure validity of data

The principal investigator assisted by some volunteer research assistants carried out data collection. The consistency of data collection was ensured by using a customised data collection sheet.

3.5.2 Reduction of bias

3.5.2.1 Selection bias:

All patients admitted consecutively from the acute care medical wards who were considered sick enough to be sent to *Siyaphila* were included in the study population. These patients were selected for transfer to *Siyaphila* based on standard criteria described in the standard operating procedure of *Siyaphila*.[2] The time of transfer of patients with different opportunistic infections was determined by standard treatment guidelines for treatment of opportunistic infections, recognized by HIV medicine clinicians.[15, 17, 19]

3.5.2.2 Information bias:

Data was validated by triangulating it from different sources in the hospital database before it was entered onto the patient data collection sheet. Double entry of all data was the standard practice for this study. The data entered onto two separate databases was manually checked and verified.

3.6 ETHICS AND PERMISSIONS

There was no patient contact during the collection of data. All collated data was anonymous as no unique patient identifiers were entered into the database. Information linking patients to the forms were kept in a separate site from the research data, confidentiality of the patients was maintained and privacy was guarded as the data

collection sheets were in a locked cabinet in the McCord Hospital research office.

3.6.1 Institutional ethics review board

The research project was registered for a 33% research project for a Master of Public Health degree with the Postgraduate Education Committee at the Faculty of Medicine, University of KwaZulu-Natal.

An application to the McCord Hospital Research Ethics committee was made and ethical approval granted (Appendix 1). A letter was sent to the committee regarding the change of title of the study.

An application to the University of KwaZulu-Natal Biomedical Research Ethics Committee was approved (Appendix 4). After review by the Postgraduate Education Committee, the protocol was submitted with a revised title.

3.6.1.1 Permission

A letter of authorization from the head of McCord Hospital has been obtained (Appendix 2).

4 CHAPTER 4: RESULTS

4.1 INTRODUCTION

In Chapter 4, the results of the data are summarised and analysed using appropriate descriptive and analytic biostatistics. The baseline characteristics of the entire cohort are described .The outcomes in the ART (exposed) and non-ART (non-exposed) groups are compared. The timing of ART initiation and outcome of those initiated on ART is described. The risk factors associated with in-hospital mortality in the ART group are presented in the univariate and multivariate analysis.

4.2 BASELINE CHARACTERISTICS OF THE ENTIRE COHORT

Four hundred and thirty two patients were admitted to McCord Hospital with AIDS and referred for subacute care to *Siyaphila*. From this group 405 (94%) were evaluated for the possibility of commencing inpatient ART, and 171 (42%) of these were initiated on ART soon after transfer to *Siyaphila* (Figure 1).The median age of those admitted for subacute care was 38 years. There were more men (55%) than women (45%) in the cohort. The majority (76%) of patients had had a CD4 count of less than 100 cells/uL. Only 9% of these PLHIV had a CD4 count >200 cells/uL. The median CD4 count for those who had this measure recorded was 28 cells/uL. (Table 1)

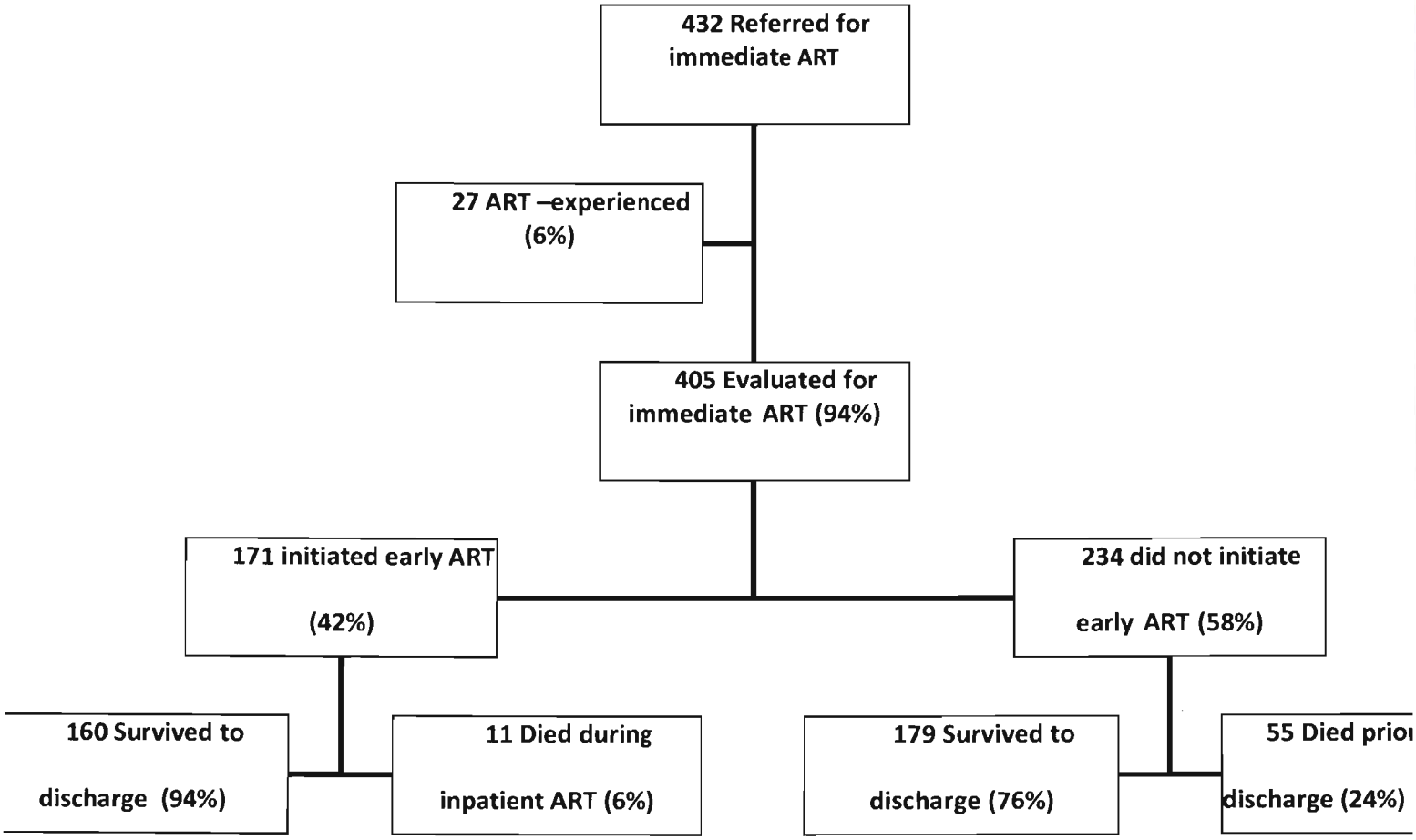

Figure 1: Flow of all patients admitted to* Siyaphila *from the McCord Hospital acute medical wards from December 2006 to August 2007

Table 1: Baseline characteristics of PLHIV admitted to *Siyaphila for* subacute care from November 2006 to August 2007 (N=405) [a]

Demographics	
Median age (years) [IQR]	38 [32-45]
Women no. (%)	182 (45)
Ethnicity No. (%)	
Black	378 (93)
Indian descent	7 (2)
Coloured	4 (1)
White	2 (1)
Not recorded	14 (3)
Laboratory parameters	
Median baseline CD4 count (cells/uL) [IQR]	28 [12-83]
Baseline CD4 cell count category (%) [b]	
0-49 cells/uL	212 (66)
50-99 cells/uL	33 (10)
100-199 cells/uL	48 (15)
200-349 cells/uL	29 (9)
Median baseline haemoglobin (g/dL [IQR] [c]	9.7 (7.6-11.3)
Median baseline albumin (g/l) [IQR] [d]	22 (17-27)

a. 27 patients were already on ART on admission

b.83 patients did not have a CD4 count recorded

c. Haemoglobin not available for 46 patients. (Normal values - Male: 11 – 14 g/dL Female: 10 – 12 g/dL)

d. Albumin not available for 86 patients. (Normal values – 25 – 35 g/dL)

4.3 COMPARISON BETWEEN THE ART AND NON ART GROUPS

405 (94%) were ART naïve and thus evaluated for the possibility of commencing inpatient ART. Only 171 (42%) of these were initiated on ART soon after transfer to *Siyaphila* (Figure 1). The rest (234, 58%) were not considered for ART for a number of irreversible medical and socio-economic reasons.

The ART group had a mean CD4 count of 55 cells/uL and the non-ART group (comprising 234 PLHIV) had a mean CD4 count of 84 cells/uL ($p<0.01$). Other baseline characteristics in both groups were similar.

The exposed and non-exposed groups had a similar proportion of opportunistic infections. The mortality before discharge from *Siyaphila* was four times lower in the ART group (11/171, 6%) compared to the non-ART group (55/234, 24 %) ($p< 0.05$) (Table 2). A significantly higher proportion of the patients who did not initiate ART during their inpatient stay died, compared to only the patients who initiated ART. This is despite the non-ART group having a higher mean CD4 count on admission. The median length of admission for patients who did not initiate ART was 13 days (mean 16 days).

Cryptococcal meningitis was the leading cause of death (15 out of 55 deaths; 27%) in the non-ART group. Out of 45 patients with cryptococcal meningitis in the non-ART group, 15 (33%) died whereas only two of 23 patients (9%) with cryptococcal meningitis in the ART group died (Table 2).

Table 2: Characteristics and outcomes of the ART (exposed) and non-ART (non-exposed) groups in the cohort of PLHIV admitted to Siyaphila between November 2006 and August 2007

	ART GROUP-171	NON-ART GROUP -234	TOTAL-405
Median age [IQR]	37 [32-46]	38 [32-35]	
Women no. (%)	83 (49)	99 (42)	182 (45)
Ethnicity no. (%)			
Black	160 (93)	218 (93)	378 (93)
Indian descent	5 (3)	2 (1)	7(2)
"Coloured"	4 (2)	4 (2)	8(2)
White	0	2 (1)	2(0.5)
Not recorded	2 (1)	5 (3)	7(2)
Mean baseline CD4 count (cells/uL) [1]	55	84 **p<0.01**	
Median baseline CD4 count (cells/uL) [IQR][1]	25 [10-78]	31 [13-105]	
Baseline CD4 cell count category no. (%)			N=322[a]
0-49 cells/uL	113 (70)	99 (62)	212(66)
50-99 cells/uL	15 (9)	18 (11)	33(10)
100-199 cells/uL	27 (17)	21 (13)	48(15)
200-349 cells/uL	7(4)	22 (14)	29(9)
Median baseline hemoglobin (g/dl) [IQR]	9.3 [7.9-11.1]	9.9 [7.4-1.5]	

a.83 did not have baseline CD4 counts recorded

Table 2 (continued)

	ART GROUP-171 (%)	NON-ART GROUP-234 (%)	TOTAL-405[b] (%)
Acute OI or complication no. (%)	n=146	N=234	N=380
Pulmonary tuberculosis	60 (42)	74 (31)	134(35)
Extra pulmonary tuberculosis	28 (19)	89 (38)	117(31)
Cryptococcus meningitis	23 (16)	45 (19)	68(19)
Pneumocystis jiroveci pneumonia	15 (10)	13 (6)	28(7)
Chronic diarrhoea (>14 days)	6 (4)	2 (1)	8(2)
Toxoplasmosis gondii	5 (3)	1 (0.5)	6(2)
HIV associated nephropathy	3 (2)	2 (1)	5(1)
Kaposi's sarcoma	3(2)	4(2)	7(2)
Other [c]	3(1)	4(2)	7(2)
Outcomes at discharge			
Early mortality prior to discharge no. (%)	11 (6)	55[d] (24) **p<0.001**	
Mortality from cryptococcal meningitis	2/23 (9%)	15/45(33%)	
Discharged home no. (%)	160 (94)	179 (76)	

b. Baseline opportunistic infection not available in 25 patients. (N is 405 – 25 = 380)

c. Other opportunistic infections were Candida oesophagitis (n=2) and herpes zoster (2) in the non- ART. In the ART group Lymphoma (2) and cardiomyopathy (1) were listed.

d. 15/55 deaths (27%) in the non-ART group were due to cryptococcal meningitis.

4.4 OUTCOMES IN THE ART GROUP

In the ART group the median duration from time of initial admission for PLHIV to the acute care medical ward to ART initiation was 14 days (IQR 11-19 days).The median duration of stay from initial admission to the acute care medical ward for PLHIV until discharge from *Siyaphila* was 18 days (IQR 15-25 days). Almost half (51%) of the patients were initiated on ART within two weeks from the time of their initial admission to the hospital. The time to initiate ART in only 28 patients (18%) was more than three weeks. Almost all the patients started on regimen 1A (Stavudine, Lamivudine, Efavirenz).

Eight patients experienced adverse events as inpatients soon after commencing ART and one patient died of drug induced hepatitis. IRIS was diagnosed in 4% of patients (n =7) post ART but caused no deaths. IRIS was related to pulmonary tuberculosis (1), extra pulmonary tuberculosis (2) and cryptococcal meningitis (2). In two cases, the opportunistic infection associated with IRIS was not recorded. Six percent (11/171) patients who initiated ART at *Siyaphila* died during the inpatient stay. Among the 11 patients who died in the ART group, pulmonary tuberculosis was the cause of death in three, extra pulmonary tuberculosis in three and cryptococcal meningitis in two of the deaths. One case each was recorded as being caused by HIV associated nephropathy HIV cardiomyopathy, and lymphoma.

Table 3 (continued):

Outcomes	Patients
Suspected IRIS	
Suspected IRIS events during inpatient ART initiation, no. (%)	7(4)
Underlying opportunistic infection among patients with IRIS [b]	
Pulmonary tuberculosis	1/7
Extra pulmonary tuberculosis	2/7
Cryptococcal meningitis	2/7
Deaths among patients with suspected IRIS syndrome	0 (0%)
Total deaths during inpatient ART initiation [c]	
Deaths, no. (%)	11 (6)
Median days to death after ART initiation (n=11) – no. [IQR]	10 [3-17]
Adverse events during inpatient ART initiation (N=171)	
Hepatitis. no. (%)	5 (3)
Renal insufficiency. no. (%)	3 (2)
Deaths among patients with suspected adverse event [d]	1 (1%)

b. Opportunistic infection was not recorded in two patients who developed a serious IRIS event

c. Pulmonary tuberculosis (n=3), extra pulmonary tuberculosis (n=3), cryptococcal meningitis (n=2), HIV associated nephropathy (n=1), HIV-associated cardiomyopathy (n=1), and lymphoma (n=1).

d. One patient died with hepatitis after ART initiation resulting from drug toxicity

Table 3: Outcomes among PLHIV enrolled for early inpatient ART (exposed group) at *Siyaphila* from November 2006 to August 2007 (N=171)

Outcomes	Patients
Timing of ART initiation	
Median duration (days) of total admission– [IQR]	18 [15-25]
Median days from initial ward admission to ART initiation [IQR][a]	14 [11-19]
Days from initial ward admission to ART initiation, No. (%)	
0-7 days	10 (6)
8-14 days	70 (45)
15-21 days	47 (31)
>21 days	28 (18)
TOTAL [a]	155 (100)
ART regimens initiated no, (%)	
D4T – 3TC – EFV	168 (98)
D4T – 3TC – NVP	2 (1)
Regimen 3A	1 (1)
TOTAL	171 (100)

a. In 16 patients, total length of stay not recorded

4.5 *TIME TO ART INITIATION AFTER DIAGNOSIS OF DIFFERENT OPPORTUNISTIC INFECTIONS*

Among the different opportunistic infections, the mean time to ART initiation from initial admission to McCord Hospital was 15 days for those with pulmonary TB and extra pulmonary TB. Patients with cryptococcal meningitis started ART after a mean of 19 days. Those with *Pneumocystis* pneumonia and chronic diarrhea commenced ART after 16 days. The longest mean time taken for ART initiation was 21 days for the five patients with Toxoplasmosis of the brain (Table 4). The mean time from admission to the acute care ward to ART initiation in the subacute care ward in all patients was 16 days. Time taken from admission to the acute care ward at McCord hospital for all infections to discharge from the Siyaphila subacute care ward was 21 days.

Table 4: Outcomes by opportunistic infection among PLHIV commenced on ART at the *Siyaphila* from November 2006 and August 2007

Opportunistic Infection	N	Time from admission to ART(median/mean days) *	Time from admission to discharge(median/mean days)
All infections [a]	137	14 / 16	18 / 21
Pulmonary tuberculosis	60	13 / 15	17 / 20
Extra pulmonary TB	28	12 / 15	17 / 19
Cryptococcal meningitis	23	18 / 19	22 / 24
P. jiroveci pneumonia	15	16 / 16	19 / 21
Chronic diarrhoea	6	16 / 16	19 / 20
Toxoplasmosis gondii	5	21 / 21	25 / 25
Other infection [b]	3	13 / 13	18 / 17

a.171 enrolled (34 excluded from analysis of time taken): 25 had no clearly recordable OIs and 9 excluded from this analysis: Kaposi's sarcoma (n=3), HIV associated nephropathy (n=3), HIV-associated cardiomyopathy (n=1) and lymphoma (2)

b. Candida oesophagitis (1) and herpes zoster (n=2)

4.6 *RISK FACTORS FOR MORTALITY IN THE ART GROUP*

Table 5: Factors associated with mortality during early exposure to inpatient ART initiation (exposed group) at *Siyaphila* from November 2006 to August 2007.

Characteristics	Univariate Inpatient mortality			Multivariate -[1] Odds Ratio (95% CI)
	N	no. (%)	p value*	
All patients	171	11 (6)		
Female	83	5 (6)		
Male	88	4 (6)	0.83	0.9 (0.2 – 4.8)
Age [a]				
≥ 40 years	63	8 (13)		
< 40 years	90	2 (2)	0.02	0.1 (0.01 – 0.9)
Opportunistic infection (OI)				
Cryptococcal meningitis	23	2 (9)		
Other OI	148	9 (6)	0.63	
CD4 cell count at initial ART failure (cells/uL)[b]				
≥ 50	49	5 (10)		
< 50	113	5 (4)	0.17	0.3 (0.05 – 1.3)
Albumin [c]				
≥ 20 g/L	104	5 (5)		
< 20 g/L	51	5 (10)	0.24	1.3 (0.2 – 7.0)
Hemoglobin [d]				
≥ 10 mg/dL	65	3 (5)		
< 10 mg/dL	101	8 (8)	0.56	
Days between admission and ART initiation [e]				
> 14 days	75	7 (9)		
0-14 days	80	3 (4)	0.17	0.4 (0.07 – 2.5)

a,b,c,d,e Missing data for categories: - due to incompletely filled information on the patient files and/or electronic records.

In the univariate analysis, the characteristics of patients initiating ART who did not survive to discharge were compared with those who survived (Table 5). In the univariate model, gender, baseline cryptococcal meningitis, CD4 cell count, albumin, haemoglobin and

days between admission and ART initiation were not predictive of very early mortality. There was a significant relationship between the age of the patient when ART was initiated and mortality before discharge. Patients 40 years and older experienced higher premature mortality compared with those less than 40 years (13% versus 2%, $P < 0.05$). The mean age of patients beginning ART who died prior to discharge was 48.2 years compared to 38.7 years among those who survived ($P < 0.05$).

A multivariate logistic regression analysis was performed only among patients who initiated ART as inpatients with the outcome variable being death prior to discharge. Covariates included gender, age, baseline CD4 cell count and presence of cryptococcal meningitis (versus other OI), albumin level, haemoglobin level and delay prior to ART initiation (less than 14 days from admission versus greater than 14 days). For each variable, odds ratios and 95% confidence intervals were calculated. Variables associated with viral suppression were included in the multivariate model. Potential interactions between variables were assessed by stratification, and combining terms in logistic regression analyses. The odds ratio for mortality for patients <40 was 0.1 (95% CI: 0.01 to 0.9) indicating that there was a significant protective effect for younger age patients commencing immediate ART in this group.

4.7 SUMMARY.

The average CD4 count is lower in patients admitted with an AIDS defining illness. There is a wide range of opportunistic infections that are common in PLHIV admitted to hospital. Tuberculosis, cryptococcal meningitis, *Pneumocystis* pneumonia and toxoplasmosis, are common in patients with low CD4 counts. The prevalence of these infections was tuberculosis (62 %), cryptococcal meningitis (17%) and *Pneumocystis* pneumonia (7 %).

Expedited ART was successfully provided at *Siyaphila*. Forty two percent of the patients were initiated on ART during the inpatient stay. The mean duration of stay for the entire group in *Siyaphila* after transfer from the acute care medical wards was 18 days. The median time from diagnosis of opportunistic infection in the acute care ward to commencement of ART at *Siyaphila* was 14 days.

ART can be safely initiated early to inpatients with TB and Cryptococcal meningitis. There were a small number of adverse events and IRIS cases reported. Immune Reconstitution Inflammatory Syndrome was an early (within one week) manifestation in only 5% of patients but none of these patients died. There was only one death in the exposed group due to drug-induced liver toxicity after ART initiation. The patients that benefited most from ART before discharge appear to be those with cryptococcal meningitis and *Pneumocystis* pneumonia There were only 2/23 (9%) deaths for cryptococcal meningitis in the ART group compared to 15/45 (33%) in the non-ART group.

Patients in the ART group had a lower CD4 count and a lower mortality and this was statistically significant. Among the patients who did not initiate ART prior to discharge the mortality was 24 %(55/234) but only six percent (11/171) among those who initiated ART. ($p<0.001$).

Age over 40 years was associated with significant mortality and PLHIV who have Stage 4 disease were found to be mostly younger (mean age of 38 years).

5 CHAPTER 5: DISCUSSION

5.1 INTRODUCTION

In the *Siyaphila* group, the initiation of ART occurred within two weeks for most opportunistic infections, including TB when the patient is admitted to hospital. The results of this retrospective study also supports the findings of published randomized control trials done in South Africa like the "SAPIT" trial for early initiation of ART(within eight weeks) in patients admitted with TB-HIV co-infection. [6] The timing for ART initiation after the diagnosis and treatment of TB in this study on 405 patients conducted at the McCord *Siyaphila* Centre was on average of two weeks. From the CAMELIA trial [23] done in Cambodia there is the growing body of evidence indicating that earlier ART in TB co-infection (within 14 days) is better. The CAMELIA study was done in 661 HIV-infected, ART-naive patients with smear-positive TB and CD4 counts <200 cells/uL (median, 25 cells/uL). The analysis of early versus late ART in SAPiT [6] is still pending, but one wonders whether simultaneous initiation of HIV and TB treatment could reduce early mortality rates even further.

Although there is increasing evidence that earlier initiation of ART may lead to reduced morbidity and mortality, multiple co-morbid illnesses, drug interactions, drug toxicities, IRIS and high pill burden complicates the management of this special group of patients. To implement expedited ART for patients presenting with acute opportunistic infection (and almost by definition advanced AIDS), prolonged hospitalization of PLHIV may be required to surmount the considerable barriers discussed. In South Africa, the care of these patients could be ideally implemented as an inpatient ART programme. The results of the *Siyaphila* programme demonstrate that early ART can be safely and efficiently initiated among patients admitted to acute medical wards.

This discussion focuses on key lessons learnt about case management of different opportunistic infections among patients admitted to a district hospital in Durban. Although McCord Hospital is a semi-private, state-aided hospital, the disease profile among

patients with stage four AIDS is similar to patients admitted to any district hospital in KwaZulu-Natal. The results of this study can contribute to further evidence to guide best practice guidelines for the public health challenges in treating large numbers of PLHIV as hospital inpatients.

5.2 CASE MANAGEMENT OF ALL THE PATIENTS ADMITTED TO THE SIYAPHILA

We describe the case management of PLHIV requiring hospital admission. The *Siyaphila* programme offers a critical additional entrance point into care for typically non-ambulatory patients with advanced disease who have been shown under routine conditions to have low ART uptake after discharge.[3] The majority of patients presented with critically low CD4 counts (two thirds below 50 cells/uL). A recent study in the academic hospital in Cape Town recommended that an improved system of inpatient initiation and earlier initiation of ART and follow up be required to improve outcomes in hospitalized HIV-infected patients. [5] The study done at the *Siyaphila* Centre of McCord Hospital resonates with this recommendation. The value of this inpatient subacute care programme is that it is linked to an acute care ward so that ART initiation can be immediate .The programme is also linked to the outpatient ART clinic of the hospital so that follow up can be appropriately managed by the same medical team.

Tuberculosis co-infection contributes the largest burden of disease and was diagnosed in two thirds of all admissions. Other common presenting infections were cryptococcal meningitis, Pneumocystis pneumonia, toxoplasmosis of the brain and chronic diarrhoea. Clinicians will need to prioritise care plans for these patients based on best practice and latest evidence as discussed in the recommendations.

5.3 MANAGEMENT OF THE INPATIENT ART GROUP

Forty-two percent of patients out of the group that were evaluated for immediate ART were found to be eligible to start ART as inpatients. This evaluation was based on biomedical and psychosocial criteria for ART readiness.[2] These patients commenced

ART after treatment for the intercurrent HIV-linked condition within a median of two weeks from date of initial admission to the hospital. This time falls within the recommended timelines set by the national guidelines for expedited ART initiation.[10]

Among the eight (5%) patients initiated on ART at *Siyaphila* who died during the in-patient stay tuberculosis (6) and cryptococcal meningitis (2) was reported the leading cause of death. This reflected the high prevalence of these opportunistic infections in PLHIV who present in an advanced stage of illness. IRIS was diagnosed in 5% of patients post-ART commencement but was not a cause of mortality. These results demonstrate that the early ART mortality due to IRIS is low and should not preclude any patient from qualifying for expedited ART initiation.

Patients with cryptococcal disease also benefited from early ART initiation within the *Siyaphila* programme as intravenous amphotericin antifungal therapy was provided as standard of care. Prior to the availability of ART, the prognosis of patients with cryptococcal meningitis was observed to be very poor. [20] It should be noted, however, that survival in the context of ART co-administration has improved a lot. [21] Evidence from the USA suggest that recurrent cryptococcal disease associated with a delay in ART initiation is associated with equal or increased morbidity and mortality. The benefits of inpatient initiation of ART in the patient with cryptococcal disease are considerable and include the opportunity to monitor the adverse renal and haematological complications of amphotericin B therapy. The benefit of a longer inpatient stay is seen in patients who started on two weeks of amphotericin B for cryptococcal meningitis as they could be counseled on adherence to therapy during hospitalization, initiated on ART before discharge and brought back to the clinic early.

The median total duration of stay in *Siyaphila* after transfer from the acute care medical wards for all patients in the ART group was 18 days (mean stay - 21 days).Most patients stayed for a median of four days after the ART initiation. This was crucial to monitor and treat anticipated adverse events and drug toxicities from combined opportunistic infection treatment and ART. The variable time to initiate ART after initial admission for different clinical conditions emphasizes the need for an individualized approach to determine the

optimal time to initiate ART. Different conditions and clinical presentations require different durations of treatment for the presenting opportunistic infection. Those patients that have associated physical and psychosocial co-morbidities require a longer time of ART readiness preparation.

Age, independent of CD4 cell count and other baseline factors, may be an important risk factor for very early (inpatient) mortality after ART initiation with the spectrum of opportunistic infections found in Durban. Age increased likelihood of death through several mechanisms including presence of co-morbid disease, greater frequency of adverse drug events or through other pathways not yet well understood. It is important to note that older patients still clearly benefited from inpatient ART initiation with a survival to discharge of 55 (87%) of 63 patients among those $\geq$ 40 years. Nonetheless, we recommend more vigilance during ART initiation in this patient group when an opportunistic infection is present.

5.4 COMPARISON OF THE ART AND NON-ART GROUP.

Fifty eight percent of patients discharged from the acute care medical wards to the *Siyaphila* Centre did not initiate ART during their admission. Seventy six percent of this non-ART group were discharged home or for follow-up at other institutions. The HIV–linked condition for which they were admitted was managed and ART readiness training was provided for them.

Twenty four percent of the patients who did not initiate ART died during their inpatient stay at *Siyaphila*. They died soon after admission due to terminal medical conditions as they presented in an advanced stage of illness .The causes of death in these patients were mainly due to tuberculosis and cryptococcal meningitis and reflect the high prevalence of these conditions on admission of this group. The mortality before discharge from the *Siyaphila* Centre was five times lower in the ART group (6%) compared to the non-ART group (24%) and this was statistically significant. There appears to be an early inpatient survival benefit for patients starting ART within two weeks of being admitted with an OI. Patients in the non-ART group were not initiated on ART because of many clinical

reasons and personal reasons. Those patients, who were terminally ill, were unable to take oral medications and had lower CD counts. Other patients in this group had relatively higher CD4 counts and were eligible for ART at *Siyaphila*. They chose to receive treatment elsewhere, were not yet willing to start ART as inpatients or were not able to afford the cost of the inpatient stay. These factors would have contributed to a higher mortality (despite the higher mean CD4 count) in the non-ART group.

Cryptococcal meningitis was the single leading cause of death in the entire non-ART group in the 15 out of 55 deaths (27%). Thirty three percent (15/45) patients with cryptococcal meningitis died in the non-ART group. This disease seems to benefit significantly from early ART initiation as soon as treatment for the infection has been completed. There were only two deaths (2/23, 9%) from cryptococcal meningitis among the ART group.(Table 2) Male patients were more numerous in this programme as more males were eligible for the ART initiation according to the criteria for admission to the programme.

5.5 LIMITATIONS OF THE STUDY

The study was conducted in 2007 and since then the policy for early counseling and testing has been revised. The national HIV counseling and testing has replaced the voluntary counseling and testing strategy in 2010.[24] This could improve the health seeking behavior of patients and many could access care earlier before serious clinical deterioration. The new guidelines [24] also provide ant tuberculosis therapy at higher CD4 counts. (<350 cells / uL) With this strategy, the mortality from tuberculosis could be significantly reduced. It will be valuable to study how the new guidelines have affected mortality among this group of patients. However where patients do still present late for care, the immediate initiation of ART can reduce mortality significantly.

A limitation of this study is that follow-up data was not available after discharge on patients initiated on ART during admission to the *Siyaphila* Centre. However, the proportion of early complications identified during this in-patient ART programme was very low. There is also a clear survival benefit in those PLHIV starting ART soon after

diagnosis of their opportunistic infections. In addition, we have seen, based on research [3] done on patients who did not enter the *Siyaphila* subacute care programme that up to a third of patients discharged after opportunistic infection and not commenced on ART would not have survived six months without the opportunity of prolonged inpatient care, including the provision of ART.

The Siyaphila programme is site specific to a subacute care unit. Not all aspects of this programme can be generalisable to all inpatients settings. However, the principles of care can be applied judiciously to any programme. One criticism we anticipate is that this programme cannot be scaled up because of cost. However, we predict cost savings in the end, because patients receiving ART will avoid incurring the high personal and societal costs of repeated hospitalisations, which typically characterize the life history of patients with advanced HIV and AIDS disease. Although the inpatient ART programme was associated with a cost, the cost of inpatient care at *Siyaphila* is actually considerably lower than the daily costs in an acute–care ward. We would recommend formal costing of the programme to determine cost per disability-adjusted life year averted. The *Siyaphila* model of care provides a high quality of clinical care in a subacute step-down facility that is likely to be at less cost than acute care due to reduction in level of staff required for implementing such a programme.

Medium and long-term adherence to ART among very sick patients in this cohort is also not known. We propose to explore this in ongoing research based from the Centre. Mortality and morbidity studies in the cohort have not been compared to the programme in outpatient settings. The comparison has also not been made with other inpatient programmes like palliative care units. However, the principles of palliative care for AIDS patients have been successfully implemented at *Siyaphila.*

6 CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

Lessons learnt about the principles of inpatient care from the published literature and the recommendations for the timing of ART from other studies need to be included in these recommendations. The *Siyaphila* programme will also provide lessons that can be applied to various inpatient settings. Recommendations will be made for the development of protocols of care for various opportunistic infections and for guidelines to develop step down care facilities linked to district hospitals.

6.1 CONCLUSIONS

6.1.1 CASE MANAGEMENT OF PLHIV ADMITTED TO A DISTRICT HOSPITAL

Average CD4 count is lower in patients admitted with AIDS defining illness. There is a wide range of opportunistic infections that are common in the wards. Tuberculosis, cryptococcal meningitis, Pneumocystis pneumonia and toxoplasmosis, are common in patients with low CD4 counts. One important challenge linked with providing an optimal service for patients are the unique needs that each patient brings to the therapeutic encounter and the need for individualised attention. Tuberculosis co-infection contributes the largest burden of disease and was diagnosed in two thirds of all admissions. Clinicians will need to prioritise care plans for these patients based on best practice and latest evidence as discussed in the recommendations. Starting ART as soon as it can be tolerated after anti-tuberculosis therapy will be of great benefit in reducing mortality.

6.1.2 INPATIENT ART PROGRAMME

The guidelines described about timing of ART initiation in the *Siyaphila* programme correlate closely with recommendations from the published literature. These patients commenced ART after treatment for the intercurrent HIV-linked condition within a median of two weeks from date of initial admission to the hospital. This time falls within the recommended timelines set by the national guidelines for expedited ART initiation.[11]

It is important to note that older patients still clearly benefited from inpatient ART initiation with a survival to discharge of 55 (87%) of 63 patients among those ≥ 40 years. Nonetheless, we recommend more vigilance during ART initiation in this patient group when an opportunistic infection is present.

The median total duration of stay in *Siyaphila* after transfer from the acute care medical wards for all patients in the ART group was 18 days (mean stay - 21 days). The variable time to initiate ART after initial admission for different clinical conditions emphasizes the need for an individualized approach to determine the optimal time to initiate ART. Most patients stayed for a median of four days after the ART initiation. This was crucial to monitor and treat anticipated adverse events and drug toxicities from combined opportunistic infection treatment and ART.

6.1.3 PATIENTS WHO WERE NOT ELIGIBLE FOR ART

For this group care was provided with the use of a multidisciplinary team that embraced holistic medical care and palliative care. An attempt was made to individualise and optimize patient care and outcomes among PLHIV. Patients in this group did not access ART for various reasons. This approach did not preclude the use of palliative care for terminally ill patients with adequate bereavement counseling and support with their families. Some patients who did not enter the programme were prepared for ART initiation and disbursed to other sites. The mortality among the patients with cryptococcal meningitis was high as reported in other studies. The patients with severe neurological complications and those in whom amphotericin antifungal therapy was contradicted generally have a very high mortality. Providing less nephrotoxic antifungal therapy and cost of care for these inpatients for prolonged periods remains a challenge.

6.2 *RECOMMENDATIONS*

6.2.1 Number 1

This study provides the basis for developing protocols for step down care in patients with advanced HIV disease. Clinicians trained in HIV medicine at McCord Hospital provided the recommendations for when to start ART after different types of opportunistic infections. These recommendations were based on published reports and guidelines for care.[25] The outcomes of this study as crucial pilot data combined with existing reports on best practice and recommendations by the South African HIV Clinicians Society [11] can form the basis for developing protocols. We think these recommendations can form the basis for further discussions of a more broadly adopted model of step down care for advanced HIV patients in South Africa.

6.2.2 Number 2

The *Siyaphila* model of care has operationalised early ART initiation described in large randomised trials reported in this paper. This retrospective analysis of inpatient care to provide early ART after OI diagnosis in 2006 and 2007 was commenced before the results of other trials were out. The programme was commenced because of the urgency of the need to reduce the mortality among this group of inpatients.

Based on evidence in the literature and best practice, the following guidelines are suggested for when to initiate ART after diagnosis of an acute opportunistic infection.

a) Pulmonary and extra pulmonary tuberculosis: Begin ART once the patient has demonstrated no early adverse effect of tuberculosis therapy as early as one week after TB treatment initiation.
b) Cryptococcal meningitis: Amphotericin B is recommended for at least 14 days with monitoring for renal dysfunction and haematological toxicity (anaemia) prior to initiation of ART.
c) *Pneumocystis* pneumonia: After a week of acute treatment, which generally will include corticosteroids and high dose cotrimoxazole, ART is recommended as early as one week after PCP therapy initiated.
d) For all other AIDS associated opportunistic infections and associated illnesses,

begin ART within a week of opportunistic infection diagnosis.

7 CHAPTER 7 REFERENCES

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8 APPENDICES

8.1 Appendix 1

McCORD HOSPITAL
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Fax: 031-2685705, Int. 273 2685705
Docex : 315 Durban
E-mail : mccords@dbn.lia.net

MCCORD RESEARCH ETHICS COMMITTEE

CLEARANCE CERTIFICATE

DATE: **21 July 2008**

STUDY NUMBER: **180708/6.1 hs**

PROJECT TITLE: **The Role of a Palliative Care In-patient Unit in Disease Management of HIV/AIDS patients admitted to a district hospital in Durban, South Africa.**

INVESTIGATOR (S): **Dr H Sunpath**

MREC DATE APPROVED: **18 July 2008**

DECISION OF COMMITTEE: **APPROVED**

Dr Helga Holst
Acting Chair: McCord Research Ethics Committee

8.2 Appendix 2

McCORD HOSPITAL
28 McCord Road,
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21 July 2008

Dear Dr Sunpath

The Role of a Palliative Care In-patient Unit in Disease Management of HIV/AIDS patients admitted to a district hospital in Durban, South Africa.

I refer to your application to undertake research at McCord Hospital. Your study proposal was reviewed by the McCord Research Ethics Committee on the **18 July 2008**.

I have the pleasure in informing you that this study has been approved.

Attached please find the Committee Clearance Certificate, with the MREC study number.

Please also complete and sign the document acknowledging the terms and conditions for undertaking research at McCord Hospital. The signed document should be returned to the Research Coordinator.

May we wish you every success in your research

Sincerely

Dr Helga Holst
Acting Chair: McCord Research Ethics Committee

New Entry

Patient Data Collection Form

Date form Completed (dd/mm/yyyy): Completed by:

Study ID number:

Date of ward admission (dd/mm/yyyy):

Date of birth: (dd/mm/yyyy)

Gender: ☐ Female ☐ Male Ethnic Group: ☐ Black ☐ White ☐ Indian ☐ Colored

Diagnosis of OI/Medical Problem:

Opportunistic Infection:

- ☐ Pulmonary Tb
- ☐ Tb Meningitis
- ☐ Extra pulmonary Tb (not Tb meningitis)
- ☐ PCP
- ☐ Cryptococcal Meningitis
- ☐ Diarrhea > 14 days
- ☐ Herpes Zoster
- ☐ Esophageal candidiasis
- ☐ Toxo gondii
- ☐ Kaposi's Sarcoma
- ☐ IRIS
- ☐ Recurrent Pneumonia
- ☐ Renal Failure
- ☐ Cardiac Failure
- ☐ CA Cervix
- ☐ Lymphoma
- ☐ ARV Complication
- ☐ Liver Toxicity (TB Drugs)
- ☐ PML
- ☐ Viral Encephalitis

- Kaposi's Sarcoma
- CMV of any organ other than liver, spleen or LN
- HIV associated dementia
- HIV associated wasting
- Viral Encephalitis
- Soft Tissue Sepsis
- Other

Baseline blood test

Latest CD4 count: _____ Date (dd/mm/yy): _____

Latest Viral load: _____ Date (dd/mm/yy): _____

Latest Hb: _____ Date (dd/mm/yy): _____

Latest Alb: _____ Date (dd/mm/yy): _____

Date of admission to Siyaphila: _____

Date of commencement of ARVs: _____

ARV Regimen:
- 3TC/D4T/EFV
- 3TC/D4T/NVP
- AZT/3TC EFZ
- AZT/3TC/NVP
- AZT/DDI/KALETRA
- AZT/DDI/EFV
- Other

Immediate/early ARV complications seen at Siyaphila (if any):
- Hepatitis
- Renal Failure

☐ Renal Failure

☐ Neuropsychiatric Complications (EFV)

☐ Other

Date Terminal Care Commenced (dd/mm/yyyy):

Outcome: ☐ Death

☐ RHT/Absconded

☐ Discharge

Referral to local clinic for: ☐ TB

☐ ARVs

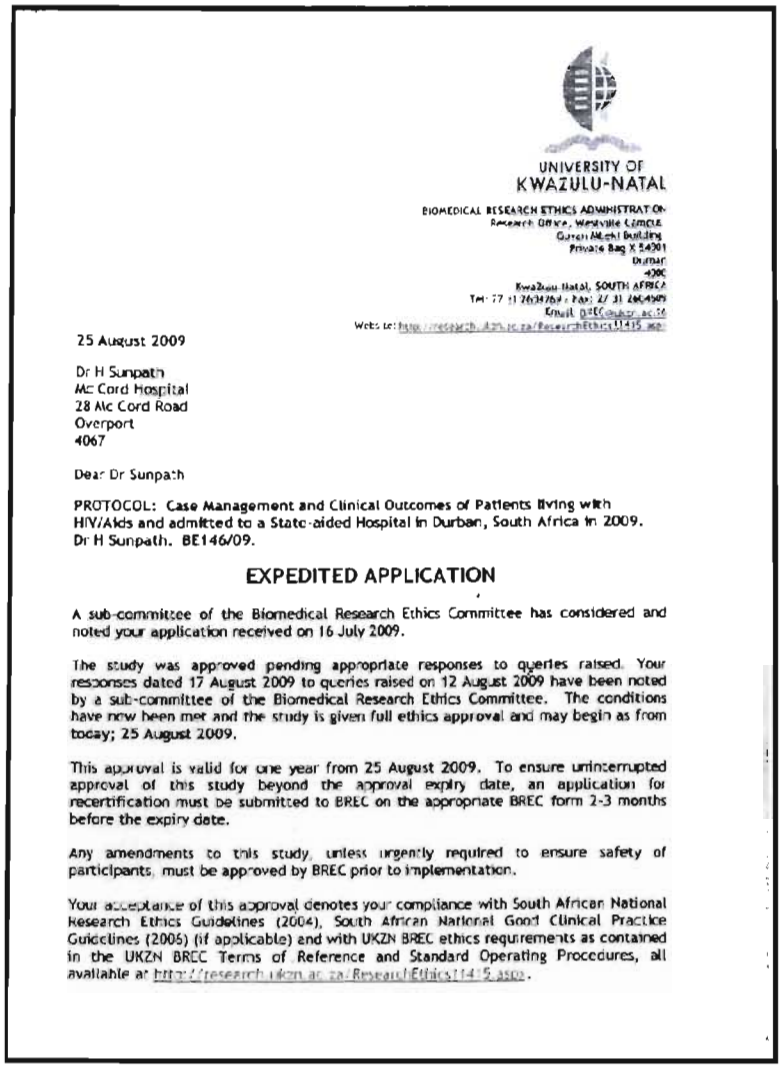
Referral for ongoing care to: ☐ HBCW

☐ The Dream Centre

Comments:

Finish

8.4 ***Appendix 4***



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25 August 2009

Dr H Sunpath
Mc Cord Hospital
28 Mc Cord Road
Overport
4067

Dear Dr Sunpath

PROTOCOL: **Case Management and Clinical Outcomes of Patients living with HIV/Aids and admitted to a State-aided Hospital in Durban, South Africa in 2009.**
Dr H Sunpath. BE146/09.

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 16 July 2009.

The study was approved pending appropriate responses to queries raised. Your responses dated 17 August 2009 to queries raised on 12 August 2009 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from today; 25 August 2009.

This approval is valid for one year from 25 August 2009. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/ResearchEthics/1415.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** at a full sitting of the Biomedical Research Ethics Committee meeting to be held on **08 September 2009.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor D.R Wassenaar
Chair: Biomedical Research Ethics Committee